

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
KRISTINA BIEKER-BRADY
CLARK & ELBING LLP
176 FEDERAL STREET
BOSTON, MASSACHUSETTS 02110-2214

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing
(day/month/year)

13 FEB 2002

Applicant's or agent's file reference
00742/062WO2

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US01/21354

International filing date
(day/month/year)

05 July 2001 (05.07.2001)

Applicant
PRESIDENT AND FELLOWS OF HARVARD COLLEGE

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.
Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

ACTION DUE Optional Art. 19 Amend.
DUE DATE 4-13-02
INITIALS J.M.

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.

19 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 20 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Authorized officer

Q. JANICE LI

Telephone No. 303-308 0196

Facsimile No. 303-305-3230

Form PCT/ISA/220 (July 1998)

ACTION DUE IDS
DUE DATE 2-13-02

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
KRISTINA BIEKER-BRADY
CLARK & ELBING LLP
176 FEDERAL STREET
BOSTON, MASSACHUSETTS 02110-2214

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing
(day/month/year)

13 FEB 2002

Applicant's or agent's file reference
00742/062WO2

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US01/21354

International filing date
(day/month/year)

05 July 2001 (05.07.2001)

Applicant
PRESIDENT AND FELLOWS OF HARVARD COLLEGE

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompany sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau.

If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication

19 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II

20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Authorized officer

O. JANICE H.

Facsimile No. 1-703-305-3230

Telephone No. 703-308-0196

Form PCT ISA 220 (July 1998)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|--|
| Applicant's or agent's file reference 00742/062WO2 | FOR FURTHER ACTION | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below |
| International application No. PCT/US01/21354 | International filing date (day/month/year) 05 July 2001 (05.07.2001) | (Earliest) Priority Date (day/month/year) 07 July 2000 (07.07.2000) |
| Applicant PRESIDENT AND FELLOWS OF HARVARD COLLEGE | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☒ Unity of invention is lacking (See Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 28.2(b), and, where applicable, it appears in Box III of the application, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☒ None of the figures

☒ because the applicant failed to suggest a figure

☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/21354

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

As required additional search fees were timely paid by the applicant, this international search report covers all searchable claims. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

Remark on Protest

☐
☐

- The additional search fees were accompanied by the applicant's protest
No protest accompanied the payment of additional search fees

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/21354

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68; C12N 5/00; C07H 21/02, 21/04

US CL : 435/6, 325; 536/23.1, 24.5; 935/1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 325; 536/23.1, 24.5; 935/1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST, MEDLINE, BIOSIS, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | FREUND et al. Host range and cell cycle activation properties of polyomavirus large T-antigen mutants defective in pRB binding. J Virology. November 1994, vol. 68, no. 11, pages 7227-7234, see entire document. | 1, 2, 7-11 |
| A | US 6,214,544 B1 (FISHER) 10 APRIL 2001, SEE ABSTRACT AND CLAIMS. | 1-11 |

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents

document published prior to the international filing date but after the priority date claimed

document member of the same patent family

Date of the actual completion of the international search

15 November 2001 (15.11.2001)

Date of mailing of the international search report

13 FEB 2002

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20530

Authorized officer

Q. JANICE H.

Facsimile No. 703/305-3230

Telephone No. 703/308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/21354

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional examination fees must be paid.

Group I, claims 1-11, drawn to a method identifying a cellular protein involved in the susceptibility to proliferative disease.

Group II, claim 12, drawn to a tumor host range virus.

Group III, claims 13-19, drawn to a method of determining gene alteration comprising determining whether a cell can act as a permissive host for the propagation of a T-HR mutant.

Group IV, claims 20-30, drawn to a method for cancer cell killing.

Group V, claims 31-42, drawn to a method for risk assessment of a proliferative disease comprising detecting alteration of a *Sal2* nucleic acid in a mammal.

Group VI, claims 43-48, drawn to a method for risk assessment of a proliferative disease comprising detecting alteration of a *Sal2* protein in a mammal.

Group VII, claims 49-52, 54, 59, 60, drawn to a knockout mouse comprising a mutation in a genomic m*Sal2* gene.

Group VIII, claims 53, 55-58, 61, drawn to a transgenic mouse whose genome comprising a nucleic acid construct including a *Sal2* gene.

Group IX, claims 62-69, 72, 74, 75, drawn to a method of identifying a compound which alters cell proliferation by measuring cell proliferation of two different abnormal test cells.

Group X, claims 70, 71, 73, 76, drawn to a method of identifying a compound which alters cell proliferation by measuring cellular *Sal2* levels.

The inventions listed as Groups I-X do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups I is drawn to a method of identifying a cellular protein, whereas group II is drawn to a tumor host range virus. Thus, they lack the same special technical feature.

The inventions listed as Groups III-VI, IX, X, and I do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups I, III-VI, IX, X are drawn to different methods, such as for identifying a cellular protein, assessing a gene alteration or cell killing. The different methods using different test criteria, different starting materials, have different method steps, different mode of operation, and different technical features. Thus, they lack the same special technical feature.

The inventions listed as Groups VI and V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups VI differs from group V in that they are different methods for risk assessment, the different method using different test criteria, i.e. a *Sal2* nucleic acid or a *Sal2* protein, the method steps and mode of operation for identifying a nucleic acid differs from that of a protein. Thus, they lack the same special technical feature.

The inventions listed as Groups X and IX do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups X differs from group IX in that they are different methods for identifying a compound, the different method using different test criteria, i.e. state of cell proliferation or levels of *Sal2* expression, the method steps and mode of operation for the two differs significantly that they lack the same special technical feature.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/21354

The inventions listed as Groups VIII and VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups VIII differs from group VII in that they are different products, a Sal2 transgene mouse and a Sal2 gene knockout mouse differs in their genomic sequence structures and phenotype. Thus, they lack the same special technical feature.

NOTES TO FORM PCT/ISA/220 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter.

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report, may be made only in connection with an amendment of that claim.

In what language?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
KRISTINA BIEKER-BRADY
CLARK & ELBING LLP
176 FEDERAL STREET
BOSTON, MA 02110-2214

PCT

INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

| | |
|--|--|
| <p>Date of Mailing (day/month/year)</p> | |
| <p>Applicant's or agent's file reference 00742/062WO2</p> | <p>PAYMENT DUE within 15 days from the above date of mailing</p> |
| <p>International application No. PCT/US01/21354</p> | <p>International filing date (day/month/year) 05 July 2001 (05.07.2001)</p> |
| <p>Applicant PRESIDENT AND FELLOWS OF HARVARD COLLEGE</p> | |

1. This International Searching Authority

(i) considers that there are 10 (*number of*) inventions claimed in the international application covered by the claims indicated below/on an extra sheet:
Please See Continuation Sheet

and it considers that **the international application does not comply with the requirements of unity of invention** (Rules 13.1, 13.2 and 13.3) for the reasons indicated below/on an extra sheet:
Please See Continuation Sheet

(ii) ☐ has carried out a partial international search (see Annex) ☒ will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.: 1-11

(iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid.

2. The applicant is hereby **invited**, within the time limit indicated above, to pay the amount indicated below:

| | | | |
|------------------------------|---------------------------------|---|---------------------------------|
| <u>\$210.00</u> | X <u>9</u> | = | <u>\$1,890.00</u> |
| Fee additional per invention | number of additional inventions | | total amount of additional fees |

The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest**, i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or

 and have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention

| | |
|---|--|
| <p>Name and mailing address of the ISA US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20530 Facsimile No. (703)305-3230</p> | <p>Authorized officer QUANICE LI Telephone No. (703)308-0196</p> |
|---|--|

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/US01/21354

This International Search Authority has found 10 inventions claimed in the International Application covered by the claims indicated below:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-11, drawn to a method identifying a cellular protein involved in the susceptibility to proliferative disease.

Group II, claim 12, drawn to a tumor host range virus.

Group III, claims 13-19, drawn to a method of determining gene alteration comprising determining whether a cell can act as a permissive host for the propagation of a T-HR mutant.

Group IV, claims 20-30, drawn to a method for cancer cell killing.

Group V, claims 31-42, drawn to a method for risk assessment of a proliferative disease comprising detecting alteration of a *Sal2* nucleic acid in a mammal.

Group VI, claims 43-48, drawn to a method for risk assessment of a proliferative disease comprising detecting alteration of a *Sal2* protein in a mammal.

Group VII, claims 49-52, 54, 59, 60, drawn to a knockout mouse comprising a mutation in a genomic m*Sal2* gene.

Group VIII, claims 53, 55-58, 61, drawn to a transgenic mouse whose genome comprising a nucleic acid construct including a *Sal2* gene.

Group IX, claims 62-69, 72, 74, 75, drawn to a method of identifying a compound which alters cell proliferation by measuring cell proliferation of two different abnormal test cells.

Group X, claims 70, 71, 73, 76, drawn to a method of identifying a compound which alters cell proliferation by measuring cellular *Sal2* levels.

1. This International Searching Authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The inventions listed as Groups I-X do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups I is drawn to a method of identifying a cellular protein, whereas group II is drawn to a tumor host range virus. Thus, they lack the same special technical feature.

The inventions listed as Groups III-VI, IX, X, and I do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups I, III-VI, IX, X are drawn to different methods, such as for identifying a cellular protein, assessing a gene alteration or cell killing. The different methods using different test criteria, different starting materials, have different method steps, different mode of operation, and different technical considerations. Thus, they lack the same special technical feature.

The inventions listed as Groups VI and V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups VI differs from group V in that they are different methods for risk assessment, the different method using different test criteria, i.e. a *Sal2* nucleic acid or a *Sal2* protein, the method steps and mode of operation for identifying a nucleic acid differs from that of a protein. Thus, they lack the same special technical feature.

Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups X differs from group IX in that they are different methods for identifying a compound, the different method using different test criteria, i.e. state of cell proliferation or levels of *Sal2* expression, the method steps and mode of operation for the two differs significantly that they lack the same special technical feature.

The inventions listed as Groups VIII and VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups VIII differs from group VII in that they are different products, a *Sal2* transgene mouse and a *Sal2* gene knockout mouse differs in their genomic sequence structures and phenotype. Thus, they lack the same special technical feature.